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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/565,230	01/20/2006	Philippe Erbs	1032751-000131	2237

21839 7590 09/05/2008

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ALEXANDRIA, VA 22313-1404

EXAMINER	
LEAVITT, MARIA GOMEZ	

ART UNIT	PAPER NUMBER
1633	

NOTIFICATION DATE	DELIVERY MODE
09/05/2008	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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Office Action Summary	Application No.	Applicant(s)	
	10/565,230	ERBS, PHILIPPE	
	Examiner	Art Unit	
	MARIA LEAVITT	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *11 June 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-31 and 35-52* is/are pending in the application.

4a) Of the above claim(s) *1-11,30,31,35-38 and 47-52* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *12-29 and 39-46* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *06 October 2003* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *12-19-2006*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Detailed Action

Applicant's response to the restriction requirement of 12-12-2007 and to the supplemental restriction requirement of 05-13-2008 has been entered.

Claim status. Claims 1-31 and 35-52 are currently pending. Applicant's election of Group II, drawn to claims 12-29 and 39-46, in Applicants' response filed on 02-04-2008, is acknowledged. Applicant's election of the following species in the reply filed on 06-11-2008 is also acknowledged:

cationic lipids as recited in claim 15,
the E1 region of the adenoviral genome as recited in claim 22,
the MVA genome as recited in claim 17,
IL-2 as recited in claims 25 and 26, IL-2 as recited in claims 42 and 47,
a viral vector as recited in claim 14, and
a poxvirus as recited in claim 16.

Claims 1-11, 30, 31, 35-38 and 47-52 are withdrawn for further consideration pursuant to 37CFR 1.142(b) as being drawn to nonelected inventions, there being no allowable generic or linking claim. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election was treated as an election without traverse (MPEP § 818.03(a)).

The requirement is still deemed proper and is therefore made FINAL.

Therefore, claims 12-29 and 39-46 are currently being examined to which the following grounds of rejection apply.

Priority

This is a 371 of PCT/IB04/02505, filed 06/29/2004, which claims priority to US Provisional application 60/508,274 filed on 10-06-2003.

Drawings objection

The drawings filed on 01-20-2006 are objected to under 37 CFR 1.83(a) because the content in the square insert in Figure 1 is unclear. Any structural detail that is essential for a proper understanding of the disclosed invention should be shown in the drawing. MPEP § 608.02(d). Corrected drawing sheets in compliance with 37 CFR 1.121(d) are required in reply to the Office action to avoid abandonment of the application. Any amended replacement drawing sheet should include all of the figures appearing on the immediate prior version of the sheet, even if only one figure is being amended. The figure or figure number of an amended drawing should not be labeled as "amended." If a drawing figure is to be canceled, the appropriate figure must be removed from the replacement sheet, and where necessary, the remaining figures must be renumbered and appropriate changes made to the brief description of the several views of the drawings for consistency. Additional replacement sheets may be necessary to show the renumbering of the remaining figures. Each drawing sheet submitted after the filing date of an application must be labeled in the top margin as either "Replacement Sheet" or "New Sheet" pursuant to 37 CFR 1.121(d). If the changes are not accepted by the examiner, the applicant will be notified and informed of any required corrective action in the next Office action. The objection to the drawings will not be held in abeyance.

Specification objection.

The disclosure is objected to because of the following informalities:

1) At page 27, lines 5-9, the specification recites:

"This cytotoxic effect can be circumvented by expressing the nucleotide sequence according to the invention encoding a UPRTase activity in the presence of uracil or by coexpressing this latter sequence with sequences encoding a CDase activity (where appropriate in fused form) in the presence of cytosine".

It is unclear how a nucleotide sequence can encode "a UPRTase activity" and "a CDase activity". It is suggested to amend the phrase to "the nucleotide sequence according to the invention encoding a polypeptide possessing an UPRTase activity". Note that the instant invention encompasses polynucleotide sequences encoding a polypeptide possessing a CDase activity derived from a native CDase by addition of an amino acid sequence, with the proviso that said polypeptide has no UPRtase or thymidine kinase activity.

2) At page 3, line 17, a comma (,) after "cells" is inappropriately followed by a period (.). Appropriate correction is requested.

3) At page 8, lines 18-19, part of the text is missing. Appropriate correction is requested.

35 USC 101-non-statutory subject matter

35 U.S.C. §101 states:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claims 12-29 and 39-46 are rejected under 35 USC §101 because the claimed invention is directed to non-statutory subject matter.

Claim 12 recites the term "a nucleic acid sequence which encodes a polypeptide according to claim 1". As written, claim 12 does not sufficiently distinguish over cells on their own right that exist naturally because the claims do not particularly point out any non-naturally occurring differences between the claimed products and the naturally occurring products,

wherein nucleotide sequences encoding a polypeptide according to claim 12 can be comprised in the DNA of a naturally occurring cell. In the absence of the hand of man, the naturally occurring products are considered non-statutory subject matter. See *Diamond v. Chakrabarty*, 447 U.S. 303, 206 USPQ 193 (1980). The claims should be amended to indicate the hand of the inventor, e.g., by insertion of "Isolated" or "Purified" as taught at page 11, lines 25-26. See MPEP 2105.

Claim Rejections - 35 USC § 112- Second Paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

Claims 16 and 17 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite in that it fails to point out what is included or excluded by the claim language.

Claims 16 and 17 are vague and indefinite in its recitation of the term "derived from" in that the metes and bounds of the term "derived from" are unclear. It is unclear the nature and number of steps required to obtain a "derivative" of a pox virus (claim 16) or a MVA virus (claim 17). The term implies a number of different steps that may or may not result in a change in the functional characteristics of a recombinant vector from the source that it is "derived from" because any given starting material can have many divergent derivatives depending on the process of derivatization. It would be remedial to amend the claim language to use the term "obtained from", which implies a more direct method of generating a recombinant vector.

Claim Rejections - 35 USC § 112- First paragraph- Lack of Enablement

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 12-29 and 39-46 rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The specification does not provide enabling disclosure for a genus of unspecified nucleotide sequences encoding a polypeptide possessing a CDase activity derived from a native CDase by addition of an amino acid sequence, with the proviso that said polypeptide has no UPRtase or thymidine kinase activity, wherein the amino acid sequence added to the CDase is derived from a polypeptide possessing an UPRTase activity. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims. To make the nucleotide sequence, as claimed, to the extent of its scope would require undue experimentation.

The factors to be considered in determining whether undue experimentation is required are summarized In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988). The Court in Wands states: "Enablement is not precluded by the necessity for some experimentation such as routine screening. However, experimentation needed to practice the invention must not be undue experimentation. The key word is 'undue,' not 'experimentation.' " (Wands, 8 USPQ2d 1404). Clearly, enablement of a claimed invention cannot be predicated on the basis of quantity of

experimentation required to make or use the invention. "Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations." (Wands, 8 USPQ2d 1404). The factors to be considered in determining whether undue experimentation is required include: (1) the quantity of experimentation necessary, (2) the amount or direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims. While all of these factors are considered, a sufficient amount for a *prima facie* case is discussed below.

Claim 12 is directed to a nucleotide sequence encoding a polypeptide possessing a CD activity derived from a native CDase by the addition of an amino acid sequence, with the proviso that said amino acid sequence derived from uracil phosphoribosyltransferase (UPRT) having UPRT activity, does not possess UPRT or thymidine kinase activity. Moreover, claims 14-26 further limit the invention to a recombinant vector comprising the claimed nucleotide sequence, claims 27-28 limit the invention to a method for preparing viral particles comprising said recombinant vector and the generated viral particle, and claims 39-46 further limit the invention to a host cell infected with said viral particle and compositions comprising said nucleotide sequence, recombinant vectors, viral particles and host cell. The specification discloses at page 6, line 2-9, that "a polypeptide according to the invention exhibits a CDase activity which is appreciably higher than that of said native CDase. Thus, the examples which follow demonstrate that the addition of an amino acid sequence which has no UPRtase activity makes it possible to increase the sensitization of the target cells to 5-FC and/or the bystander effect induced in the

treated animal. The factor by which the sensitization is increased is advantageously at least 2, preferably at least 5 and, very preferably, 10 or more". Therefore, the instant claims are broadly interpreted as comprising a genus of nucleotide sequences and/or variants encoding for a polypeptide possessing any level of CDase activity by the addition of any number of amino acids derived from a polypeptide possessing UPRT activity, with the proviso that the encoded polypeptide does not possess UPRtase or Thymidine Kinase activity. Since the amino acid sequence of a protein determine its structural and functional properties, predictability of which changes can be tolerated in a protein's amino acid sequence and obtain the desired activity requires knowledge of an guidance with regards to which amino acids in the protein's sequence, if any, are tolerant of modification and which are conserved (i.e. expectedly intolerant to modifications), and detailed knowledge of the ways in which the proteins' structure relates to its function. The same is true of a polynucleotide sequence, as the nucleic acid sequence of the polynucleotide directly correlates with the amino acid sequence of the polypeptide. However in this case this disclosure does not provided sufficient guidance for the breadth of the nucleic acid sequences claimed and it would require undue experimentation to determine a genus of sequences meeting the claimed requirements.

The specification discloses the *Saccharomyces cerevisae* FCY1 gene and the *E.*coli *codA* genes encode the native CDase in the respective two organisms (p. 3, lines 5-8). In addition, the specification teaches the *upp* and FUR1 coding for the UPRTase of *E.*coli and S. c*erevisae,* respectively. Moreover, the specification discloses in the art at the time of filing, the generation of fusion proteins coding a two-domain enzyme possessing CDase and UPRTase activities, and demonstrates *in vitro* that the transfer of a hybrid *codA::upp* or FCY1::FUR1 gene, carried by an

expression plasmid, increases the sensitization of transfected B16 cells to 5-FC (p. 4, lines 1-14). Furthermore, the specification states at page 4, lines 22-29, "The present invention provides a more efficient polypeptide, thereby making it possible to increase the sensitivity of cells to 5-FC or the bystander effect induced by the production of 5-FU and to improve the prospects for gene therapy using suicide genes". Furthermore, the specification discloses at page 5, lines 16-30, that sequences substantially identical to SEQ ID No. 1 are "very appropriate for implementing the invention". Specifically, the specification as filed evidences in Example 1 the generation of FCU1-8 by direct mutagenesis of the gene FCU1 by replacing at position 183 an Arg by a Ser using site directed mutagenesis (p. 28, lines 30-35). However, the specification is silent about the identity of the nucleotide sequence in plasmid pCI-neoFCU1 and whether the sequence encodes a polypeptide of SEQ ID NO:1 (e.g., cytosine deaminase) to which the amino acid sequence of SEQ ID NO:2 (e.g., uracil phosphoribosyltransferase) has been fused in frame, or merely a modified nucleotide sequence encoding the polypeptide of SEQ ID No.1 with both UPRTase and CDase activities. Furthermore, the specification exemplifies how the Argl83 change in Ser in gene FCU1 leads to a loss in UPRTase activity without modifying CDase activity in the generated gene Fcul-8 (p. 30, lines 5-10). While the plasmid pCI-neo Fcul-8 is taught in the specification which conserves CDase activity but losses UPRTase activity, no examples are disclosed of mutations other than Arg183, or addition of amino acids or what domains or regions of the claimed polypeptide are required for functional loss in UPRTase activity without modifying CDase activity. There is no teaching regarding which part of sequences of the FCU1 gene has UPRTase and CDase activities. Hence, the specification is silent about mutations in the gene FCU1 leading to loss of UPRTase activity while conserving CDase activity, let alone

addition of of amino acids of any length to the gene FCU1 resulting in a gene encoding a polypeptide with the claimed functionally.

At the effective filing date, the art clearly teaches the construction of vectors encoding a fusion protein expressing both, functional cytosine deaminase and uracil phosphoribosyltransferase (Buchsbaum et al., US Patent 6,552,005; Date of Patent April 22, 2003). Indeed, Buchsbaum et al., discloses that "another factor that may limit CD/5-FC efficacy is the intratumoral expression of dihydropyrimidine dehydrogenase (DPD), the rate-limiting enzyme in 5-FU catabolism" (col. 33, lines 37-40). Moreover, the author adds, "To overcome this potential limitation, a replication-defective Ad vector was constructed encoding a fusion protein between CD and an additional enzyme, uracil phosphoribosyltransferase (UPRT, AdCDUPRT). UPRT catalyzes the first step in 5-FU anabolism, the production of 5-fluoruridine monophosphate (5-FUMP). It was hypothesized that simultaneous expression of CD and UPRT may overcome intratumoral DPD expression by shunting CD-produced 5-FU away from the DPD-dependent catabolic pathway and into the UPRT-mediated anabolic pathway" (col. 33, lines 47-57). Likewise, Erbs et al., (US Patent 7,049,117, Date of Patent May 23, 2006) discloses isolated polynucleotides encoding a two domain enzyme possessing both CDase and UPRTase activities as well as a mutant of the UPRTase encoded by the FUR-1 gene having the first 35 residues deleted, e.g., mutant FCR1 Δ105 exhibiting UPRTase activity which is greater than that of the native enzyme (col. 3, lines 17-25). Moreover, Erbs et al., teaches that "the fusion protein which is produced by the hybrid FCY1:: FCR1 Δ105 gene, which results from the in-frame fusion of the FCY1 and truncated FUR1 genes, retains its UPRTase activity but exhibits a CDase activity which is increased by a factor of 10 to 30 as compared with that measured using the

native FCY1 product" (col. 3, lines 16-48). Therefore, the art of record, while teaching polynucleotides encoding a fusion protein with CDase and UPRTase activity, is silent about polynucleotides encoding a fusion protein with CDase and loss of UPRTase activity with the contemplated use of delaying or inhibiting cancer or tumor progression. In addition, at the time of filing, the recombinant technology for the generation of new protein fragments was highly developed. However, the ability to determine *a priori* whether a mutation will generate a functional fragment was not. The skilled artisan understands that one nucleotide change in a DNA molecule or one amino acid change in the polypeptide encoded by the DNA molecule could result in the loss of its biological activity as demonstrated in the generation of sickle-cell anemia wherein on specific amino acid mutation gave rise to the inherited disease (Biochemistry, John Wiley and Sons, 1990, p. 126-129). Even single-nucleotide polymorphism without affecting the amino acid sequence can affect folding of the protein and thus alter its function (Kimchi-Sarfaty et al., 2007, Science, pp. 525-528; p. 527, col. 3, last paragraph). The disclosure does not provide enough guidance for any nucleotide mutation and/or additions leading to a polypeptide with loss of UPRTase activity while retaining CDase activity.

As set forth above by the nature of the invention, neither the prior art of record nor the as-filed specification provides sufficient guidance to enable a person skilled in the art to generate a nucleotide sequence encoding a polypeptide possessing a CDase activity, said polypeptide derived from a native CDase by the addition of an amino acid sequence, with the proviso that said polypeptide has not UPRTase, wherein said amino acid sequence added to the native CDase is derived from a polypeptide possessing an UPRTase activity with the contemplated therapeutic use of reducing tumor size. Though the plasmid pCI-neo Fcul-8 is disclosed in the specification

as encoding a polypeptide exhibiting CDase activity but with loss of UPRTase by changing the Arg183 into serine in the FCU1 gene, there is not sufficient disclosure about the identity of the nucleotide sequence in the FCU1 gene, and whether this gene encodes for the polypeptide of SEQ ID No. 1 and SEQ ID No. 2, or encodes a mutant form of SEQ ID No. 1. In addition the art of record only discloses isolated polynucleotides encoding a two domain enzyme possessing both CDase and UPRTase activities used to delay or inhibit cancer or tumor progression. Since, it would require undue experimentation to identify other peptides comprising CDase activity but with loss of UPRTase with the contemplated use of reducing the size of tumors, it certainty would require undue experimentation to make their corresponding DNA and, therefore, claims encompassing a genus of nucleic acids that may encoded for a polypeptide possessing a CDase activity with a loss in the UPRTase activity are not enabled by the claimed embodiment

As the result, given the unpredictability of the art and the lack of working example in the instant specification, particularly when taken with the lack of guidance in the specification, it would have required undue experimentation to practice the instant invention without a predictable degree of success to identify an enormous number of nucleotide sequences as broadly or generically claimed, with a resultant identification of sequences comprising the contemplated activity.

Conclusion

Claims 12-29 and 39-46 are rejected.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Maria Leavitt whose telephone number is 571-272-1085. The examiner can normally be reached on M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph Woitach, Ph.D can be reached on (571) 272-0739. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

To aid in correlating any papers for this application, all further correspondence regarding his application should be directed to Group Art Unit 1633; Central Fax No. (571) 273-8300. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

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/Maria Leavitt/

Maria Leavitt, PhD
Examiner, Art Unit 1633